REMARKS

Claims 2-5, 7-21 and 51-55 are pending in the present application. Claims 22-50 have been cancelled. Claims 2 and 10-13 have been amended. Claims 51-55 have been added. Claims 14-17 and 21 have been allowed. No new matter has been added.

CLAIM REJECTIONS

DRAWINGS

Applicants acknowledge with appreciation that the Formal Drawings filed February 12, 2003 have been approved by the Official Draftsperson.

RESPONSE TO AMENDMENT

Applicants note with appreciation that the Examiner has withdrawn the rejection of claims 1-21 under 35 U.S.C. §112, second paragraph.

ALLOWABLE SUBJECT MATTER

Applicants note with appreciation that the Examiner has allowed claims 14-17 and 21.

THE 35 U.S.C. §102 REJECTIONS

The Examiner has maintained the rejection of claims 2, 5, 7-13 and 18-20 under 35 U.S.C. §102(b) as being anticipated by US Patent No. 5,629,159 ("Anderson") as evidenced by Kilby *et al.*, *Trends Genet.* 9: 413-421, 1993 ("Kilby"). Specifically, the Examiner states that claimed nucleic acid molecule has the same structural limitations as the nucleic acid molecule taught by Anderson. The Examiner also states that although Applicant's argument (that Anderson does not teach or suggest inversion of a recombinase gene or expression control sequence) is noted, the claims are not limited to inversion of a recombinase gene or expression control sequence (*see*, Office Action at page 4).

Applicants have herewith amended claims 2 and 10-13 to recite a nucleic acid molecule comprising a first and a second signal sequence that are positioned to mediate inversion of either

a recombinase gene or the expression control sequence when the signal sequences are contacted with a recombinase, which decreases or eliminates recombinase-mediated toxicity. Anderson teaches the excision of an immortalization gene using a first and second recombinase signal sequence where the sequence can be LoxP or FRT. However, Anderson does not teach or suggest the inversion of either a recombinase gene or an expression control sequence. Kilby teaches that an excised nucleic acid would be quickly lost *in vivo*. Applicants note that Kilby alone or in combination with the teachings of Anderson, does not teach or suggest the inversion of either a recombinase gene or an expression control sequence or the decrease or elimination of recombinase-mediated toxicity following inversion of either a recombinase gene or the expression control sequence when the signal sequences are contacted with a recombinase.

Further, new claims 51-55 added herein are not anticipated by Anderson or Kilby. New claim 51 depends from claim 2 and therefore contains all the limitations of claim 2, and new claims 52-55 are directed to a cell comprising two nucleic acid molecules wherein the first nucleic acid comprises a first signal sequence and the second nucleic acid comprises a second signal sequence wherein when the signal sequence are contacted with a recombinase strand exchange is mediated between the two nucleic acid molecules. Neither Anderson nor Kilby teach or suggest a signal sequence on different nucleic acid molecules, which, when contacted with a recombinase, mediate strand exchange between the two nucleic acid molecules.

Thus, because Anderson and/or Kilby do not teach or suggest all of the limitations of the claimed invention. Applicants assert that claims 2 and 10-13, as amended herein (and claims 5, 7-9 and 18-20, which depend from claim 2) and new claims 51-55, as added herein, are not anticipated by Anderson as evidenced by Kilby. Therefore, this rejection of these claims should be withdrawn.

The Examiner has maintained the rejection of claims 2-4, 7 and 8 under 35 U.S.C. §102(b) as being anticipated by either one of WO 97/06271 ("Choulika") as evidenced by US Patent 6,200,800 ("Choulika '800") or Russ *et al.*, *J. Virol.* 70(8): 4927-4932 ("Russ") as evidenced by Kilby. Specifically, the Examiner states that claimed nucleic acid molecule has the same structural limitations as the nucleic acid molecule taught by Choulika and Russ.

As discussed above, Applicants have amended claim 2 to recite a nucleic acid molecule comprising a first and a second signal sequence that are positioned to mediate inversion of either a recombinase gene or the expression control sequence when the signal sequences are contacted with a recombinase, which decreases or eliminates recombinase-mediated toxicity. Choulika and Russ teach a loxP site in the 3'LTR sequence U3 with the gene to be inserted into a cell. Choulika and Russ do not specifically teach the inversion of either a recombinase gene or of an expression control sequence. Moreover, Kilby teaches that an excised nucleic acid would be quickly lost *in vivo* and Choulika '800 teaches that a recombinase system can include CreLox sites or FLP sites. However, neither reference, alone or in combination with the teachings of Russ and Choulika, respectively, teaches or suggests the inversion of either a recombinase gene or an expression control sequence or the decrease or elimination of recombinase-mediated toxicity following inversion of either a recombinase gene or the expression control sequence when the signal sequences are contacted with a recombinase.

Further, new claims 51-55 added herein are not anticipated by Choulika as evidenced by Choulika '800 or Russ as evidenced by Kilby. New claim 51 depends from claim 2 and therefore contains all the limitations of claim 2, and new claims 52-55 are directed to a cell comprising two nucleic acid molecules wherein the first nucleic acid comprises a first signal sequence and the second nucleic acid comprises a second signal sequence wherein when the signal sequence are contacted with a recombinase strand exchange is mediated between the two nucleic acid molecules. Choulika as evidenced by Choulika '800 or Russ as evidenced by Kilby do not teach or suggest a signal sequence on different nucleic acid molecules, which, when contacted with a recombinase, mediate strand exchange between the two nucleic acid molecules.

Accordingly, Applicants assert that claim 2, as amended herein (and claims 3-4, 7 and 8, which depend from claim 2) and new claims 51-55, as added herein, are not anticipated by Choulika as evidenced by Choulika '800 or by Russ as evidenced by Kilby. Therefore, the rejection of these claims should be withdrawn.

The Examiner has also maintained the rejection of claims 2, 5, 7-13 and 18-20 under 35 U.S.C. §102(a) as being anticipated by Bunting *et al.*, *Genes & Development* 13(12): 1524-1528, 1999 ("Bunting") as evidenced by Kilby. Specifically, the Examiner states that the claimed

nucleic acid molecule has the same structural limitations as the nucleic acid molecule taught by Bunting.

As discussed above, Applicants have amended claim 2 to recite a nucleic acid molecule comprising a first and a second signal sequence that are positioned to mediate inversion of either a recombinase gene or the expression control sequence when the signal sequences are contacted with a recombinase, which decreases or eliminates recombinase-mediated toxicity. Bunting teaches a nucleic acid molecule comprising a first and second recombinase signal sequence flanking a recombinase encoding sequence as well as the transformation of ES cells with such a described nucleic acid molecule. Bunting further teaches that a neomycin resistance gene can be positioned between the recombinase signal sequences such that expression of the recombinase excises the neomycin resistance gene. Bunting does not specifically teach the inversion of either a recombinase gene or of an expression control sequence. Kilby teaches that an excised nucleic acid would be quickly lost *in vivo*. Thus, Kilby, alone or in combination with the teachings of Bunting, does not teach or suggest the inversion of either a recombinase gene or an expression control sequence or the decrease or elimination of recombinase-mediated toxicity following inversion of either a recombinase gene or the expression control sequence when the signal sequences are contacted with a recombinase.

Further, new claims 51-55 added herein are not anticipated by Bunting or Kilby. New claim 51 depends from claim 2 and therefore contains all the limitations of claim 2, and new claims 52-55 are directed to a cell comprising two nucleic acid molecules wherein the first nucleic acid comprises a first signal sequence and the second nucleic acid comprises a second signal sequence wherein when the signal sequence are contacted with a recombinase strand exchange is mediated between the two nucleic acid molecules. Neither Bunting nor Kilby teach or suggest a signal sequence on different nucleic acid molecules, which, when contacted with a recombinase mediate strand exchange between the two nucleic acid molecules.

Thus, Bunting and/or Kilby do not teach all of the limitations of the claimed invention. Accordingly, Applicants assert that claim 2, as amended herein (and claims 5, 7-13 and 18-20, which depend from claim 2) and new claims 51-55, as added herein, are not anticipated by Bunting as evidenced by Kilby. Therefore, this rejection of these claims should be withdrawn.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

Ivor R. Elrifi, Reg. No. 39,529
Christina V. Karnakis, Reg. No. 45,899
Attorneys for Applicant
c/o Mintz, Levin
One Financial Center
Boston, MA 02111
Telephone: (617) 542 6000
Fax: (617) 542 2241

Dated: July 7, 2003